PATENT
Attorney Docket No. 272478US0XPCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
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SEVE, M. and FAVIER, A.) Group Art Unit:
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Serial No.: 10/535,395) Examiner: EWOLDT, Gerald R.
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Filed: 04/10/2006)
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For: PROTEIN SPECIFIC TO PANCREATIC BETA CELLS IN ISLETS OF LANGERHANS AND APPLICATIONS THEROF

Declaration pursuant to 37 C.F.R. § 1.132

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

I, Alain FAVIER, do hereby declare and state the following

1. That I am a Pharmacy Doctor, and that I received a Bachelor's degree in Chemistry, a Master's degree in Human Biology and a PhD in Biochemistry (University of Grenoble, France). Presently, I am the head of the Center for Innovation in Biology (University Hospital of Grenoble, France), as well as an emeritus professor at the Faculty of Pharmacy of Grenoble (in Biochemistry and Clinical Biochemistry). Enclosed, please find a copy of my *curriculum vitae* and a list of scientific publications, which clearly indicate my expertise in the fields of zinc transporters and diabetes.

2. I am one of the inventors of the above-captioned patent application and therefore I am very familiar with the subject application. I have read and understood the latest Official Action issued by the U.S. Patent and Trademark Office on 04/24/2008. It is my understanding that Claims 39 to 48 were rejected under 35 U.S.C. § 101, as lacking patentable utility. In rendering this rejection, the Examiner asserts that neither the claims nor the specification disclose any reason for the detection of autoantibodies to ZnT-8 or fragments thereof.

3. In order to address the issue of utility concerning the detection of autoantibodies directed ZnT-8 or the disclosed fragments thereof, I would like to recall some points

concerning the present application, and concerning the knowledge of the skilled artisan in the field of diabetes at the date of filing of the present application:

4. **Disclosure of the present application**

The present application describes ZnT-8 as a beta-cell specific protein, which can consequently be used as a new marker for beta cell selective sorting and counting. The fact that ZnT-8 is specifically expressed in the beta cells of the pancreatic islets of Langerhans is disclosed in the present application, at least in the very first paragraph and page 6, lines 24-27.

The claims have been amended to reflect this, by reciting that the autoantibodies which are detected are specific for the beta cells of the pancreatic islets of Langherhans.

Besides, I respectfully note that contrary to the Examiner's assertion, the word "autoantibody" appears in the specification, at least at page 20, third paragraph.

5. **Since many years, the skilled artisan has known of the link between beta cell mass, autoimmunity and type 1 diabetes**

It is clearly known since years that Type 1 diabetes is an autoimmune disease resulting from specific destruction of the insulin-producing beta cells of the Langerhans islets of the pancreas (Cell 85:291–297 (1996), copy of which is enclosed). Two phases can be distinguished: insulitis, when a mixed population of leukocytes invades the islets; and diabetes, when most beta cells have been killed off, and there is no longer sufficient insulin production to regulate blood glucose levels, resulting in hyperglycaemia.

It has been demonstrated that physiological destruction of beta cells is a crucial event at disease outset, initiating autoimmunity against these cells (Nature 414:792-798 (2001), copy of which is enclosed).

6. **At the date of filing of the present application, the skilled artisan knew that auto-antibodies directed against beta-cell antigens could be used as markers of type 1 diabetes**

I would like to draw the Examiner's attention towards two publications which more precisely reflect the general knowledge of diabetologists at the time when the present application was filed.

The first publication is a commentary, entitled "*Autoimmunity and Diabetes*", published in 1999 in the *Journal of Clinical Endocrinology and Metabolism* (Kukreja and Maclaren, 1999, copy of which is enclosed). In this article, the authors have reviewed what was known in 1999 about type 1 diabetes, also called immune-mediated diabetes (IMD). Their review encompasses several aspects of IMD, such as genetics, pathogenesis and future prospects regarding the diagnosis and treatment of IMD.

As explained by Kukreja and Maclaren (see page 4373, right column, lines 4-21 and 34-46), IMD results from the destruction of beta cells of the islets of Langerhans, which is a chronic process. At the time of clinical diagnosis of IMD, about 80% of the beta cells have been destroyed, but autoantibodies to beta cells are detectable long before a person develops diabetes. Most importantly, the progression of the disease is quite variable after the onset of islet cell autoimmunity, since some patients rapidly progress to clinical diabetes, while others remain in a non-progressive state. It appears that the nature, intensity, and antigenic spreading of the reactivity of these autoantibodies distinguish individuals who develop diabetes from those who do not. Indeed, antigenic/epitope spreading of the autoantibody responses is one important marker of impending progression, because those with a single autoantibody progress slowly, whereas those with autoantibodies to multiple antigens most often progress rapidly. First discovered with respect to ICA plus insulin autoantibodies, the principle extends to all antibody markers. Diabetes risk and time to diabetes in relatives of patients, thus, directly correlates with the number of different autoantibodies present.

At the end of this review, the authors anticipated that novel important target antigens for T cells that attack the islets of Langerhans would be discovered, as well as appropriate markers to detect autoimmune response of type 1 diabetes in the general population (page 4377, left column, line 26-38).

The second article is a review article published in 2001, entitled "*Prediction and Diagnosis of Type-1 Diabetes Using β-cell Autoantibodies*" (Batstra *et al.*, *Clinical Laboratory*, 2001). In this article, the authors explain that early diagnosis of diabetes, or prognosis before the clinical manifestations become detectable, is important for avoiding macro- and micro-vascular complications due to the deterioration of metabolic control (see at least in the abstract). Batstra *et al.* also mention that discrimination between type 1 and type 2 diabetes is important for determining the most appropriate treatment, and that this can be performed by detecting autoantibodies targeting beta cells of the islets of Langerhans (see page 499, left column, 1st paragraph).

Batstra *et al.* define the "secondary prediction" as a prediction of type 1 diabetes mellitus based on the detection of β-cell-directed autoantibodies in individuals in the prediabetic phase (see page 500, left column). It appears that this prediction is more efficient when combining several antibody tests, especially because of epitope spreading (see page 501, right column, before-last paragraph, and the paragraph bridging pages 501 and 502).

7. **At the date of filing of the present application, diagnostic assays based on the detection of autoantibodies directed against beta-cell antigens were intensively developed**

The diagnostic assay standardization program reported in Diabetes 50:1749-54 (2001) also shows that routine diagnosis of type 1 diabetes based on beta cell-specific auto-antibodies was being implemented before the date of our patent filing.

8. **At the date of filing of the present application, the skilled artisan, reading the specification, would immediately have recognized the utility of detecting autoantibodies to ZnT-8 and fragments thereof**

Since our patent application clearly describes ZnT-8 as a beta-cell specific protein, and since the skilled artisan in the field of diabetes perfectly knew, at the date of filing of the present application, that auto-antibodies directed against beta-cell specific antigens could be used as markers for the prognosis and diagnosis of type 1 diabetes, the skilled artisan, reading the present specification, would have immediately found useful to detect anti-ZnT-8 autoantibodies, at least in sera from prediabetic and diabetic patients, to confirm that the auto-antibodies could be used as a prognosis/diagnosis marker.

Experiments conducted since the filing of the present application indeed confirmed that detection of auto-antibodies directed against ZnT-8 is useful because it reflects the autoimmune process in a patient enduring type I diabetes. In particular, the amount of autoantibodies directed against ZnT-8 or its fragments reflects the number of beta cells still functional, *i.e.*, beta cell mass, and hence provides important information about the diabetes state.

As a conclusion, I am truly convinced that the claimed method is supported by a substantial asserted utility, because the skilled artisan, at the date of filing, would have found valuable reasons for detecting autoantibodies to ZnT-8 and fragments thereof.

9. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and emprisonment, or both under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

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PÔLE BIOLOGIE
Département de Biologie Intégrée
Responsable Pr. A. FAVIER

Date 26 Sept 2008

Alain FAVIER

Encl.: - CV and list of publications

- Batstra, M. R., Aanstoot, H. J., and Herbrink, P. (2001). Prediction and diagnosis of type 1 diabetes using beta-cell autoantibodies. Clin Lab 47, 497-507.
- Kukreja, A., and Maclaren, N. K. (1999). Autoimmunity and diabetes. J Clin Endocrinol Metab 84, 4371-4378.

- Mathis, D., Vence, L., and Benoist, C. (2001). beta-Cell death during progression to diabetes. Nature 414, 792-798.
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- Tisch, R., and McDevitt, H. (1996). Insulin-dependent diabetes mellitus. Cell 85, 291-297.

Curriculum

Favier Alain Emile

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Official actual positions:

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Graduation

Pharmacist, Bachelor in Chemistry, Master in Human Biology, PhD in Biochemistry (University of Grenoble)

Research Activities

Past-Director of the Magister in Health Biotechnology and Master in Biotechnology of the Grenoble University
Coordinator of the research network on free radicals CERLIB
Vice-Coordinator of the research project SUVIMAX
Member of the French board of the Society for Free Radical Research
Member of the international committee TEMA (Trace in Man and Animal)
Member of the national network on Nutrition and Cancer: NACRE
Member of the IMBG (Institut Métaux en Biologie de Grenoble)
Editor or member of the editorial committee of the journals:
Biological Trace Element Research, Journal of Trace Elements , Journal of Trace Elements in Experimental Medicine, Journal of Nutritional and Environmental Medicine, Annals of Nutrition and Metabolism

Scientific production

Research field: trace elements, oxidative stress, DNA damage, antioxidants, clinical biology

331 papers in international journals

210 invited lectures to scientific meetings

390 free communications

editor of 2 scientific books in French and 5 in English

Papers of Professor Favier for the last 5 years, restricted to Diabetes or zinc

BOUVARD S, FAURE P, ROUCARD C, FAVIER A, HALIMI S.
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JOURDAN E, EMONET-PICCARDI N, DIDIER C, BEANI J, FAVIER A, RICHARD M.
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